UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/735,608 | 12/12/2003 | Marcel P. Bruchez | 5100-0702.20 | 1956 |

20855 7590 05/18/2006

ROBINS & PASTERNAK
1731 EMBARCADERO ROAD
SUITE 230
PALO ALTO, CA 94303

| EXAMINER | |
|---|---|
| DO, PENSEE T | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1641 | |

DATE MAILED: 05/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| **Advisory Action Before the Filing of an Appeal Brief** | **Application No.** 10/735,608 | **Applicant(s)** BRUCHEZ ET AL. | |
|---|---|---|---|
| | **Examiner** Pensee T. Do | **Art Unit** 1641 | |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 03 March 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1,3-16 and 38-41*.
   Claim(s) withdrawn from consideration: *17-37*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

LONG V. LE 05/12/06
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

## *Advisory Action*

### *Claim Status*

Claims 1, 3-41 are pending. Claims 1, 3-16, 38-41 are being examined.

Claims 17-37 are withdrawn from further consideration according to Ochiai Guidelines.

### *Information Disclosure Statement*

The information disclosure statement (IDS) submitted on April 18, 2006 was filed after the mailing date of the final action on December 29, 2005. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

### *Maintained Rejection(s)*

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-7, 10-13, 16, 38, 39, 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi et al. (US 6,306,610) in view of Rothbard et al. (US 6,306,993).

Bawendi teaches a composition comprising fluorescent semiconductor nanocrystals associated to a molecule such as cells, prokaryotic or eukaryotic. The semiconductor nanocrystals comprise a CdSe core and a ZnS shell. The composition is

also associated with cell membranes. (see col. 3, line 60-col. 4, line 62; col. 19, lines 58-60; col. 20, lines 51-59; col. 29, lines 41-42).

However, Bawendi fails to teach the nanoparticle is associated with a cationic polymer capable of enhancing the transport of the semiconductor nanoparticle across a biological membrane; wherein the cationic polymer has from 5 to 25 contiguous Lys and/or Arg residues. Bawendi also fails to teach a kit comprising a semiconductor nanoparticle complex according to claims 1, 12, 16 and instructions for preparing the encoded cells using the semiconductor nanoparticle complex. Bawendi also fails to teach the cationic polymer is a tat peptide from protein transduction domain of the HIV tat protein.

Rothbard teaches methods and composition for transporting drugs and macromolecules across biological membranes wherein the biological membranes are contacted with a conjugate containing a biologically active agent that is covalently attached to a transport polymer. Such transport polymer has 6 to 25 subunits of L-Arginine. The transport enhancing polymers are exemplified by peptides in which arginine residues constitute the subunits. Exemplary eukaryotic cell membranes of interest include membranes of dendritic cells, epithelial cells, endothelial cells, keratinocytes, muscle cells, fungal cells, bacterial cells, plant cells and the like. Biological active agents are macromolecules such as nucleic acids, peptides, proteins and analogs thereof. The agent may be linked to the polymer by a linking moiety. The composition includes a conjugate containing a biological active agent covalently attached to at least one transport polymer and can be packaged with instructions for

using it. (see col. 2, line 44-col. 4, line 45; col. 5, lines 47-58). The transport polymers contain short-length polymers from 6 to 25 subunits. The conjugate is effective to enhance the transport rate of the conjugate across the biological membrane relative to the transport rate of the non-conjugate biological agent alone. (see col. 6, line 63-col. 7, line 5). Detecting uptake of macromolecules may be facilitated by attaching a fluorescent tag. (see col. 11, lines 3-4). Fluorescently labeled peptide polymers composed of 6 or more arginine residues entered cells more efficiently than the tat sequence 49-57 in fig. 1 (see col. 11, lines 30-40). Since the polymer of Rothbard composes of 6 to 25 contiguous Arg residues, it must be a cationic polymer.

Since Bawendi and Rothbard both teach using a label such as nanocrystals for cells or cell membrane, it would have been obvious to one of ordinary skills in the art to associate the polymer, which comprises of 6 to 25 subunits of Arg residue, taught by Rothbard to the nanocrystals as a fluorescent label and use in the composition of Bawendi because macromolecules such as peptides and oligonucleotides experience difficulty in passing across the biological membrane and having a polymer as that of Rothbard enhances trans-membrane transport. Furthermore, the nanocrystals of Bawendi can be used a label which associates with the polymer to so that measures of biological molecules transported across the biological membrane can be easily detected because the nanocrystals of Bawendi associates with the biological membrane. Regarding claims 38, 39 and 41, it would have been obvious to one of ordinary skills in the art to package the combined composition taught by Bawendi and Rothbard with

instruction for using it for economical convenience since Rothbard teaches packaging the polymer with biological active agent into a kit with instructions for using it.

Claims 8, 9, 14, 15 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bawendi et al. (US 6,306,610) in view of Frankel et al. (US 5,652, 152).

Bawendi has been discussed above.

However, Bawendi fails to teach that the cationic polymer is tat peptide from the protein transduction domain of the HIV tat protein and a kit comprising the composition of claim 14 with instruction of using. Bawendi also fails to teach the sequence ID NO. 1 comprising of Arg Lys Lys Arg Arg Gln Arg Arg Arg.

Frankel teaches intracellular delivery of cargo molecules by the use of transport polypeptides which comprise HIV tat protein or one or more portions thereof and which are covalently attached to the cargo molecules. The transport polypeptides are characterized by the presence of the tat basic region (amino acids 49-57). The biological active cargo molecules such as polypeptides, nucleic acids are delivered/transported into the cytoplasm and nuclei of cells in vitro and in vivo. (see abstract). Label such as a fluorescent was used to study the transported molecules across the cell membrane. The label is attached to the tat peptide. (see col. 42, lines 24-29). Frankel teaches sequence ID No. 4, amino acids 12-20, comprising Arg Lys Lys Arg Arg Gln Arg Arg Arg. (see col. 55-56, sequence ID. NO. 4).

It would have been obvious to one of ordinary skills in the art to use the HIV tat peptide for transporting biological molecules across the cell membrane as taught by

Frankel and attach it to a fluorescence semiconductor nanocrystal which associates to a cell membrane so that when biological molecules to be transported reach the cell membrane, they can be transported effectively and efficiently with the aid of the tat peptide and their activity or measurement can be detected by the nanocrystals since the nanocrystals have a spectral emission that is tunable to a desired wavelength, and wherein said wavelength provides information about a biological state or event. It would have been obvious to one of ordinary skills in the art to package the combined composition into a kit with instruction of using it for economic convenience since Frankel teaches that the tat polypeptide can be used as research laboratory reagents, either alone or as part of a transport polypeptide conjugation kit. (see col. 7, lines 30-32).

***Response to Arguments***

Applicant's arguments filed March 3, 2006 have been fully considered but they are not persuasive.

Applicants submit the same arguments as addressed in the previous response. Furthermore, Applicants argue that the secondary references, Rothbard and Frankel, use convention fluorophores, which have no physical resemblance to a semiconductor nanocrystal and thus cannot provide the motivation to combine the transport peptide with a semiconductor nanocrystal.

Rothbard and Bawendi teach using labels such as fluorescent labels to detect activity within a cell. Bawendi teaches that the fluorescent semiconductor nanocrystals can be used to visualize location in a cell. (see col. 22, lines 30-34). Rothbard teaches that the fluorescently labeled peptide polymers or the transport peptide linked polymer is

used to assess cellular uptake of biological molecules being transported across the cell membrane. (see col. 11, lines 3-33). Frankel also teaches using fluorescent label to study the transported molecules. The label is attached to the tat peptide. (see col. 42, lines 24-29). Thus, one of ordinary skills in the art would have been motivated to combine these references based on those teachings above of Bawendi and Rothbard, or Bawendi and Frankel. Fluorescent tags can be used to assess the cellular uptake of biomolecules and nanocrystals in Bawendi is a fluorescent label. Thus, one of ordinary skills in the art would have reasonable expectation of success when linking the fluorescent nanocrystal of Bawendi to a transport peptide of Rothbard or Frankel. Applicants argue that "There is absolutely no reason to believe that the carrier peptides employed to transport organic molecules across biological membranes would also successfully transport inorganic nanocrystals across biological membrane". Rothbard and Frankel teach the same transport polymer as the claimed invention, and that such polymer can be linked to a fluorescent tag. Bawendi teaches the same fluorescent semiconductor nanocrystal as the claimed invention and it is a fluorescent tag. Thus, one of ordinary skills in the art would have success in combining these references. If Applicants argue that the transport polymer of Rothbard and Frankel cannot transport inorganic nanocrystal across a biological membrane, then it is no difference that Applicants are admitting that the present invention is not enable. Although, the fluorescent tags of Rothbard and Frankel do not have physical resemblance to the semiconductor nanocrystal, the fluorescent tags of Rothbard and Frankel can emit fluorescent such as the fluorescent nanocrystal of Bawendi. One of ordinary skills in the

art would use the either the conventional fluorescent tag or the nanocrystal of Bawendi in order to compare which label gives a more efficient signal through experimentation routine.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 571-272-0819. The examiner can normally be reached on Monday-Friday, 7:00-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Pensee T. Do
Patent Examiner
May 3, 2006